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In re Patent Application of	**MAIL STOP RCE**
William Freeman	Group Art Unit: 1612
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For: PHOTODYNAMIC THERAPY FOR OCULAR NEOVASCULARIZATION	

DECLARATION UNDER 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I am an inventor of the above-identified application.

2. It is my understanding that the reference: Jampol et al., "Treatment of Juxtafovial Chroidal Neovascularization in the Era of Photodynamic Therapy With Verteprofin," Am. J. of Ophthamol., Vol. 134, No. 1, pp.99-101, July 2002, is being cited as prior art against the pending claims.

3. The present application claims priority to provisional application no. 60/419,883, filed October 18, 2002.

4. Jampol et al. was published on-line on June 25, 2002 (see Exhibit A attached hereto), less than 5 months prior to Applicants' priority date and thus is available as a reference under 35 U.S.C. 102(a).

5. The Jampol et al. reference is not prior art or a prior invention to Applicants' claimed invention, having been published after conception and reduction to practice of Applicants' invention.

6. Applicants conceived and reduced the invention described in the pending application to practice prior to the publication of Jampol et al. Attached hereto is a evidence of the conception and reduction to practice of Applicants' claimed invention at least as early as May 7, 2001 (see, e.g., Exhibit B, attached hereto).

7. Accordingly, Applicants' conception and reduction to practice of the claimed invention predates the Jampol et al. reference. Thus the reference is not prior art to Applicants' claimed invention.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements were made on information and belief and are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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William R. Freeman M.D.

EXHIBITS A & B

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Editorial

Treatment of juxtafoveal and extrafoveal choroidal neovascularization in the era of photodynamic therapy with verteporfin*[1]

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Article Outline

- References

Photodynamic therapy (PDT) using verteporfin is now a well-established treatment modality for selected patients with subfoveal choroidal neovascularization (choroidal neovascularization under the center of the foveal avascular zone). Randomized clinical trials have shown evidence of benefit of this treatment in patients with predominantly classic subfoveal

EDITORIAL

Treatment of Juxtafoveal and Extrafoveal Choroidal Neovascularization in the Era of Photodynamic Therapy With Verteporfin

LEE M. JAMPOL, MD AND LANCE SCOTT, MD

PHOTODYNAMIC THERAPY (PDT) USING VERTEPORFIN is now a well-established treatment modality for selected patients with subfoveal choroidal neovascularization (choroidal neovascularization under the center of the foveal avascular zone). Randomized clinical trials have shown evidence of benefit of this treatment in patients with predominantly classic subfoveal choroidal neovascularization (CNV) in age-related macular degeneration (AMD),[1] in occult with no classic subfoveal neovascularization in AMD,[2] or subfoveal CNV in patients with pathologic myopia.[3] In addition, an uncontrolled case series suggests possible benefit for patients with subfoveal CNV from presumed ocular histoplasmosis syndrome (POHS). In fact, retina specialists throughout the world are utilizing this therapy for patients with many additional causes of subfoveal CNV, including idiopathic CNV, angioid streaks, multifocal choroiditis, and serpiginous choroiditis (Rosenfeld PJ. Expanding indications for PDT. Presented at the American Academy of Ophthalmology Retina Subspecialty Day November 9, 2001, New Orleans, LA).

See also pp. 62–68 and 137–139.

What is the role, if any, for PDT with verteporfin in patients with CNV that is juxtafoveal (CNV not under the center of the fovea but less than 200 μ from the center) or extrafoveal (CNV more than 200 μ from the center of the fovea)? Although very little clinical research has been done in this area, PDT with verteporfin should be considered for the therapy of CNV that is not subfoveal in certain selected situations. This should be done despite the fact that it is presently not approved for use, by the U.S. Food and Drug Administration or compensated by the Centers for Medicare and Medicaid Services (CMS) for use in these patients. This editorial reviews these situations.

Juxtafoveal CNV is a common cause of visual loss in patients with AMD, pathologic myopia, POHS, idiopathic CNV, multifocal choroiditis, and other entities. The Macular Photocoagulation Study (MPS) clearly demonstrated the value of krypton thermal laser for juxtafoveal CNV secondary to AMD, POHS, and idiopathic CNV.[4] For other types of juxtafoveal CNV, considerable anecdotal evidence exists suggesting the value of thermal photocoagulation. For myopic CNV that is juxtafoveal or extrafoveal, thermal laser photocoagulation initially appears to be helpful but a growth or creeping of the scar and delayed degenerative changes may cause delayed visual loss.[5] For all types of CNV treated with thermal laser, persistence and recurrence of the CNV are problems often resulting in poor visual outcomes. There are other treatment modalities for CNV available, including systemic, periocular or intraocular corticosteroids, submacular surgery (including macular translocation), transpupillary thermotherapy, radiation, and the use of various angiogenesis inhibitors. For the purposes of this editorial we will consider only thermal laser and PDT with verteporfin as having proven benefit for CNV. Additional research will add other modalities.

What should be the role of PDT with verteporfin for juxtafoveal lesions? Not all juxtafoveal membranes are the same. Some juxtafoveal membranes just barely enter the foveal avascular zone. They resemble extrafoveal choroidal neovascularization and thermal laser is not technically difficult to perform. The results are favorable, likely similar to those with extrafoveal membranes. In this situation, the present use of PDT with verteporfin in most patients is probably not wise, as we know well the value of thermal laser and have little experience with PDT with verteporfin. Randomized trials comparing PDT with verteporfin with

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Dr. Jampol is a consultant for Novartis Ophthalmics/QLT as a member of the Data and Safety Monitoring Committee for studies of photodynamic therapy of choroidal neovascularization.

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thermal laser for extrafoveal membranes and just barely juxtafoveal membranes are indicated. Until then, thermal laser should usually be the treatment of choice.

Other juxtafoveal membranes are very close to the center of the foveal avascular zone, and treatment with thermal laser has a high risk of damaging the center of the avascular zone. In this situation, the membrane resembles a subfoveal membrane and consideration of PDT using verteporfin is reasonable. These observations concerning juxtafoveal CNV apply to AMD, myopia, POHS, and other neovascular membranes.

There are some situations where use of PDT with verteporfin is particularly tempting. For example, thermal laser produces an absolute scotoma, whereas PDT with verteporfin may allow survival of the retina over the CNV. Thermal laser photocoagulation in a patient with reading vision, depending on the involved eye, where the resulting scotoma will be just to the left of fixation, may result in great difficult reading posttreatment. Successful PDT with verteporfin may allow a better outcome. In each patient, the treating ophthalmologist must assess the risk of direct damage to the central vision by the thermal laser, evaluate the likely effects of PDT with verteporfin, and then decide on PDT vs thermal laser.

There are juxtafoveal membranes that do not do well with thermal laser photocoagulation. The MPS showed that for patients with systemic hypertension and AMD with juxtafoveal CNV, thermal laser was no better than the natural history.[4,6] These patients may have a more favorable outcome using PDT with verteporfin, and it should be considered. The MPS also showed that accurate, complete, and intense treatment of the choroidal neovascular membrane contributed to a favorable outcome.[7] This was particularly true for the POHS, with the CNV less than 200 μ from the center of the avascular zone, where accurate and complete treatment resulted in 5% severe visual loss vs 25% with partially untreated or wider than indicated borders of treatment. For AMD it was more difficult to determine if accurate and complete treatment of CNV with thermal laser was of benefit. If the clinical situation does not allow accurate and complete treatment, especially with POHS, consideration should be given to PDT with verteporfin. This might include patients with hazy media (e.g., cataract), treatment of juxtafoveal CNV in children or in patients unable to hold steady (e.g., tremor), or unable to cooperate (e.g., dementia). It would include patients where an adequate fluorescein angiogram cannot be accomplished (e.g., fluorescein allergy, hazy media).

For juxtafoveal CNV secondary to diseases where the visual outcome is not as bleak as in patients with AMD (this might include idiopathic CNV and polypoidal choroidal vasculopathy) thermal laser treatment of juxtafoveal membranes may have a greater risk than the natural history. In these cases, PDT with verteporfin may be warranted.

How well does PDT with verteporfin work for juxtfoveal and extrafoveal CNV? We presently have little data. It has been suggested that some patients in the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study who had improvement in vision with PDT with verteporfin actually had juxtafoveal CNV, not subfoveal CNV (N. Bressler, MD written communication, Jan. 30, 2002). While we await additional clinical trials, it seems logical that the efficacy of treatment with PDT with verteporfin will be better with extrafoveal membranes than with subfoveal, with juxtafoveal CNV intermediate. What we clearly do not know is whether these PDT outcomes for extrafoveal and juxtafoveal lesions are better than use of thermal laser photocoagulation.

It is possible that the combination of thermal laser and PDT with verteporfin might be more beneficial than either alone. For example, for a juxtafoveal or extrafoveal membrane it might be possible to first do PDT with verteporfin and then see if the patient responds. If the lesion continues to grow, then thermal laser could be considered. Similarly, it may be possible to do thermal laser first and if recurrence occurs (which augurs a much worse prognosis), then PDT with verteporfin could be considered. The treatments could also be performed at the same session. These possibilities suggest additional research protocols. Combinations with other treatments (e.g., corticosteroids, antiangiogenic drugs) also seem desirable for future studies.

Photodynamic therapy with verteporfin is an important part of our armamentarium in treatment of subfoveal CNV. At the present time, it is appropriate to consider its use for juxtafoveal CNV very close to the center of the fovea in patients who cannot cooperate for accurate and complete treatment by thermal laser, when the photocoagulation scotoma may impair vision in a patient with only one eye with reading vision, when fluorescein angiography cannot be performed, when hazy media preclude adequate thermal photocoagulation, in AMD patients with systemic hypertension, or for treatment of juxtafoveal CNV in patients with a better prognosis. The clinician should make a decision for each patient with juxtafoveal or extrafoveal CNV based on the known risks and benefits of thermal laser, PDT with verteporfin, or other treatment modalities. Additional clinical trials are indicated to guide these decisions.

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PROPRIETARY INFORMATION

TECHNOLOGY TRANSFER and INTELLECTUAL PROPERTY SERVICES, UCSD INVENTION AND TECHNOLOGY DISCLOSURE FORM

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Create a short title describing the general nature of the invention without revealing the specific details that would enable others to reproduce the invention (e.g., new anticancer compound, method for chip fabrication, etc.). Please limit the title to 60 characters.

Photodynamic therapy enhanced Feeder vessel treatment of choroidal neovascularization in age related macular degeneration

B. UCSD INVENTOR(S)

*List all UCSD employees or students who **intellectually** contributed to the invention. Please also indicate any joint or special appointment with non-UCSD institutions (e.g., VA and HHMI) in the "Position" box.*

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C. INVENTORS NOT AFFILIATED WITH UCSD

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D. FUNDING SOURCES FOR THE PROJECT UNDER WHICH THE INVENTION WAS MADE

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This information is important for deciding priority of invention and/or legal "bars" to patenting. In general, publications, in any medium, before the date a formal patent application is filed in a national patent office can cause a bar to patent filing in most foreign countries. While United States patent law allows inventors up to one year to file a patent application after the first publication, public use, or sale, the loss of foreign rights is often very important to potential industrial licensees.

EVENTS	DATE	INDICATE THE WRITTEN RECORD (e.g., notebook, letter, email). IF ORAL DISCLOSURE, INDICATE TO WHOM.
1. Initial conception of the idea		
2. First description of complete invention, oral or written		
3. First successful demonstration (first actual reduction to practice)		
4. Has this work been: i. submitted for publication? Y N ii. accepted for publication? Y N iii. Published? Y N		
5. Have you presented this work at a conference or meeting? i. Did you submit an abstract? Y N ii. Was abstract published? Y N iii Name of conference or meeting? Y N i. Did presentation include handouts? Y N		

G. INVENTORS' SIGNATURES

By signature below, I acknowledge my responsibilities and rights to royalty-sharing under the current University of California Patent Policy.

William A Freeman 5/7/01

Inventor signature Date

Inventor signature Date

Inventor signature Date

H. WITNESS - invention disclosed to and understood by:

Witness signature Date

Print witness name

Inventor signature _____ Date _____

I. ABOUT THE INVENTION

Please write a summary of the invention following the numbered guidelines listed below. Since this information will be used to determine patentability, commercial uses, and potential licensees of the invention, please provide as many details as possible. If you have a written manuscript descriptive of your invention, please also attach a copy to this form.

1. What exactly does your invention do?

The invention is a concept to use photodynamic therapy to enhance Feeder vessel treatment of choroidal neovascularization in age related macular degeneration. To do this we propose to use imaging technology such as the HRT (Manu: Heidelberg instruments) to localize the feeder vessels in conjunction with an intravenous dose of photodynamic therapy activated by a laser light. Subsequently we propose to eventually deliver the treatment light focally through or in conjunction with the images generated by the HRT scan to most precisely localize the feeder vessel treatment. This can be combined with image stabilization technology to allow treatment during any eye movements thus enabling treatment without anesthetic injection in the region.

2. What is unique, novel, or better about your invention as compared to existing art?

This invention combines 3 different technologies, a patented drug along with photodynamic treatment and image stabilization technology. This is a novel approach for Feeder vessel treatment of choroidal neovascularization in age related macular degeneration.

3. What is the existing art to which you are comparing?

Recent advances in retinal imaging using confocal scanning laser ophthalmoscopes have made it possible to treat feeder vess which perfuse choroidal neovascular iplexes in age related macular degeneration patients. Although it is sometimes possible to close these feeder vessels, there are multiple vessels and they typically are difficult to close entirely. They also usually re-open. Photodynamic therapy does allow closure of subretinal neovascular membranes, however the light and drug dose parameters for these therapies have to be adjusted downward into a safe range to avoid a retinal photodynamic lesion. The use of higher dose photodynamic therapy parameters would allow more permanent closure of the pathologic vessels but with some overlying retinal toxicity. This would be acceptable if the treatment was over feeder vessels as these are typically not under the fovea.

4. Describe how your invention works (or may work). Please include drawings, schematics, figures, etc., necessary to explain how the invention works or may work.

5. Describe the stage of development of the invention (e.g., concept stage, experimental data stage, computer model simulation stage, working prototype stage, etc.). Please include data, photographs, etc., indicating the stages of development.

6. What are potential commercial applications of your invention?

Novel treatment for choroidal neovascularization in age related macular degeneration

J. COMPANIES

Based on your knowledge, please provide the names and addresses of companies that are, or may be, interested in manufacturing, using, and/or further developing your invention.

Company & Contact Name	Company Address

K. Please list or attach any literature references that most closely describe the state of the related art before your invention. If possible, please consider doing a search of the literature, because it will help in the evaluation of your invention.

K. If a company is interested in licensing your invention, would you be interested in assisting or working with the company to develop your invention into a product under a sponsored or research agreement with the University? Y / N

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Abstract:

Verteporfin enhanced feeder vessel therapy in subfoveal choroidal neovascularization secondary to age-related macular degeneration

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Key Words: macular degeneration, photodynamic therapy, choroidal neovascular membrane, feeder vessel

ABSTRACT

Purpose: To investigate the safety and efficacy of extrafoveal photodynamic therapy (PDT) occlusion of feeder vessels in patients with choroidal neovascularization due to age-related macular degeneration.

Design: A consecutive case series at one retina center.

Methods: Feeder vessels were identified using dynamic fluorescein and indocyanine green angiography with scanning laser ophthalmoscope. Standard dose of verteporfin and laser wavelength were used. The dose was escalated by increasing the duration of the light dose so the light regimen was 50 J/cm^2 (83 sec. duration) for patients 1 and 2, 100 J/cm^2 (166 sec. duration) for patients 3,4,5 and 125 J/cm^2 (208 sec. duration) for patients 6 and 7.

Results: Patients were examined at weeks 1,4 and 12 after the treatment. The mean improvement on EDTRS chart 3 months after treatment was an increase of 2.6 lines (p=.075). Elimination of the lowest light dose showed significant improvement (p=.030) between pre- and post-PDT visual acuity. Closure of the feeder vessel was achieved angiographically in 2 eyes, in 2 eyes the feeder vessel was hypoperfused and in 3 eyes the vessels were vessels were neither closed nor hypoperfused. At the last follow up all feeder reperfused. There was no evidence of retinal damage outside the treatment spot.

Conclusion: Verteporfin enhanced feeder vessel therapy does not cause retinal damage and may have potential to improve central vision in subfoveal choroidal

neovascularization due to exudative macular degeneration. Further studies at high doses of light are warranted for efficacy of this novel therapeutic strategy.

INTRODUCTION

Choroidal neovascularization (CNV) is responsible for most of the severe vision loss associated with age-related macular degeneration (AMD)(1). The concept of treatment of subfoveal neovascular membranes in AMD by specifically targeting its feeder (afferent) vessel has been considered an attractive therapeutic approach in order to avoid collateral damage to larger retinal areas adjacent to and involving the fovea (2-7). The initial clinical success with absence of histopathologic data on treated choroidal neovascularization feeder vessels led to elaboration of a theoretical model of choriocapillaris blood flow and its relation with CNV (8).

According to this model choroidal neovascularization feeder vessels lie in the Sattler layer and enter the choriocapillaris in close proximity to the other penetrating vessels that form the choriocapillaris/CNV communication. This has been supported by clinical observations (9). Previous studies also demonstrated that 22-42% of patients with CNV have demonstrable feeder vessels (2,3). A feeder vessel is seen to perfuse the choroidal neovascular membrane and can be distinguished from a draining vein by high speed videoangiography and timing. Published reports suggest that these vessels, when successfully photocoagulated by laser, produce reduction of the associated CNV blood flow. It has been reported that even partial occlusion of

a feeder vessel may be sufficient to effectively reduce CNV blood flow and cause a favorable clinical response (4).

Various methods of laser feeder vessel obstruction have been employed including the 630 nm red (1), the 576 nm yellow (2,7), the 514 nm argon green (3), the 810 nm diode laser (7,10,11) and photodynamic therapy (PDT)(12). Feeder vessels are typically extrafoveal and thus higher light doses (prolonged duration of treatment) may allow even more complete destruction of feeder vessels as collateral damage to overlying retina is less of a visual safety concern. In this FDA-approved pilot study we investigated the safety and efficacy of extrafoveal photodynamic therapy (PDT) occlusion of feeder vessels in patients with CNV due to AMD with escalation of light dose.

SUBJECTS and METHODS

Patient population

This is a phase I-II light-dose escalating study approved by the Institutional Review Board of the University of California San Diego. The patients were seen at the Jacobs Retina Center in La Jolla, California between August 2003 and December 2004. Patients signed informed consents that comply with US Regulations and the International Conference on Harmonization guidelines prior to undergoing any study-related procedures.

All patients had fluorescein angiographic (FA) evidence of minimally classic CNV with high-speed indocyanine green (ICG) documentation of a single extrafoveal feeder vessel. Inclusion criteria in the study were age more than 50 years and the presence of CNV in the study eye. In the case of eligibility of both eyes only one eye was to be treated, the decision being made between the patient and physician. Patients had to have best-corrected visual acuity (VA) score in the study eye between 65 and 20 letters measured with an Eartly Treatment Diabetic Retinopathy Study (ETDRS) chart (Lighthouse Inc., New York, NY) which is an approximate Snellen equivalent of 20/50 to 20/400. For the purpose of statistical analysis we transformed Snellen acuity into the logarithm of the minimum angle of resolution (logMAR) equivalent to create a linear scale of visual acuity (logMAR=log[1/Snellen equivalent]). Extrafoveal feeder vessels supplying the area of the CNV lesion had to be clearly identified with the greatest

linear dimension of the entire lesion less than 5400 microns at the initial treatment. The patients had to be able to return for all study visits.

Excluded were the patients with hypersensitivity/allergy to fluorescein, ICG or verteporphin, with the feeder vessel located directly beneath a major retinal artery or vein, the patients unable to be photographed (media opacity, non-compliance or lack of venous access) or the patients with other ocular diseases associated with CNV (angioid streaks, pathologic myopia, histoplasmosis, blunt trauma, multifocal choroiditis). Additional exclusion criteria were pregnancy, prior PDT for minimally classic or occult with no classic CNV and prior or ongoing treatment for AMD (macular scatter laser photocoagulation, subfoveal laser photocoagulation, transpupillary thermotherapy, radiation or pharmacotherapy).

FV identification

At the baseline visit, all of the patients underwent a general ophthalmologic evaluation with dilated exam. Dynarnic FA and ICG examinations were performed using the Heidelberg HRA I scanning laser ophthalmoscope (SLO) (Heidelberg Engineering, Heidelberg, Germany). The SLO is configured to record ICG fluorescence at a rate of 12 frames/second with a two second frame buffer. High-speed video ICG angiography was used to identify feeder vessels in the presence of CNV. The identification of feeder vessel(s) was based on their appearance preceding that of the retinal vessels during the early phases of dynamic FA and ICG and on their relationships with choroidal circulation and the CNV during the course of the angiography (1,2) (Fig. 1a, 1b, 1c). After the feeder vessel has been identified on the H-S ICG the corresponding spot of area to be treated is transposed on to early an FA image to facilitate the location of laser delivery. The eligible patients were those with a single feeder vessel identified and therefore only one vessel was treated.

Treatment

The treatment procedure started with intravenous infusion of verteporfin 6 mg/m^2 administered during 10 minutes. Fifteen minutes after the end of infusion, photocoagulation energy was delivered by 689 nm laser light with the following

range of parameters: light intensity 600 mW/cm^2, laser spot size 1000-2000 microns (used at the discretion of the investigator depending on the size of feeder vessel). The dose was escalated by increasing the duration of the light dose so the light regimen was 50 J/cm^2 (83 sec. duration) for patients 1 and 2, 100 J/cm^2 (166 sec. duration) for patients 3,4,5 and 125 J/cm^2 (208 sec. duration) for patients 6 and 7 (Table 1). The light application was interrupted at constant time intervals to give the patient a chance to blink and rest. In order to keep the fractionation of the light delivery controlled, the light treatment was stopped every 83 sec. (every 50 J/cm^2 delivered) and commenced exactly 30 sec. later. The treatment, all performed by one investigator (WRF), was followed by sun protective precautions (13).

Follow-up

Patients returned for follow-up at weeks 1,4 and 12 after the treatment. The complete ophthalmologic exam included ETDRS visual acuity (VA), intraocular pressure measurement, dilated fundus exam, stereoscopic fundus photography and FA/high-speed ICG videoangiography (week 4 and 12 post-treatment). The primary study objective at these visits was to assess the safety of extrafoveal PDT. The secondary objective was to assess preliminary signs of efficacy of this treatment as measured by the extent of reduction of the CNV membrane on ICG, closure of FV on videoangiography, reduction or absence of

leakage determined by FA and change in VA from baseline. The area of leakage on fluorescein angiogram was delineated using Eye Explorer Software Version 1.3.2.0. The pre- and post-treatment findings were compared using one-tailed paired t-tests.

RESULTS

The study included 7 eyes of 7 patients (3 men) with average age (mean±SD) 79.57±5.07 years. After the procedure we evaluated the degree of occlusion or reduction of perfusion of the feeder vessel by scanning laser videoangiography, presence or change in late leakage from CNV on FA and visual acuity.

Of the treated patients two received PDT with 50 J/cm^2, three 100 J/cm^2 and two patients 125 J/cm^2 light dose (Table. 1). None of the patients reported any adverse effect related to injection or post-treatment course. On ophthalmoscopic examination in none of the treated eyes did we observe increase in exudation, hemorrhage or laser-related damage of the fovea or perifoveal area.

Pre-treatment VA ranged from 20/50 (0.4 logMar) to 20/400 (0.05 logMar) (median 0.829 logMar). Visual acuity after the treatment ranged from 20/32 (0.625 logMar) to 20/200 (0.1 logMar) (median 0.585 logMar)(p=.075). One patient (14.2%) lost one line, two patients (28.6%) gained 1 line, two patients (28.6%) gained two lines and two patients (28.6%) gained three lines of vision on EDTRS chart 3 months after treatment. On average, patients after therapy gained 2.6 lines (13 letters). Elimination of the lowest light dose showed significant improvement (p=.030) between pre- and post-PDT VA results.

The first post-treatment videoangiography showed that closure of the feeder vessel was achieved in 2 eyes (28.5%)(Fig.1b), in 2 eyes (28.5%) the feeder vessel was hypoperfused (Fig.2b) and in 3 eyes (43%) feeder vessels were neither closed nor hypoperfused (Fig. 3b). At the last follow up all feeder vessels were reperfused (Figs. 1c, 2c, 3c). The pre- and post-treatment area of fluorescein leakage on FA was 12.44 ± 11.75 mm^2 and 10.78 ± 9.73 mm^2, respectively (p=.122). When eliminating the lowest energy dose there was a difference between pre- and post-treatment leakage area (p=.054). Pre- and post-laser intensity of fluorescein leakage in the area of leakage was difficult to judge because the electronic gain on FA in patients varied and is not standardized.

DISCUSSION

Treatment of subfoveal neovascular membranes by treating the feeder vessel(s) supplying the membrane has been investigated in an effort to preserve the vision loss associated with exudative AMD. Because of the morphologic features of the posterior choroid, the feeder vessels are not easily visible with conventional still-frame ICG angiography. The advances in high-speed ICG angiography have made it possible to more precisely identify feeder vessels, the successful demonstration of which ranges between 22-42% even when angiography is analyzed by experienced retinal specialists (2,3).

Photocoagulation of feeder vessels in AMD-associated CNV with different types of lasers resulted in various amounts and duration of anatomic and functional stabilization (3,5-7,9). Feeder vessel closure initially used argon green (3) and then yellow dye (2) lasers. The goal of these treatments was to use a hemoglobin absorbing wavelength to damage feeder vessels. Such photocoagulation caused full thickness retinal damage and choriocapillaris damage as well (2,3). Subsequently, the 810 nm diode laser (7,11) was studied because of its ability to penetrate tissue and potentially spare the overlying retina. With this wavelength, vascular closure is difficult because the laser is poorly absorpbed by hemoglobin (14) and coupling the laser with ICG as a desirable photosensitizing agent was suggested to make this modality more

effective. However, even with this approach, early reperfusion of treated FV ensues in both humans and animals (10).

Photodynamic therapy has shown statistical benefit both in classic and occult choroidal neovascularization (15,16). As demonstrated by ICG angiography verteporfin therapy has vaso-occlusive mechanism that affects both the CNV and normal choroid (17). The same study reports that a single PDT application produces an area of hypofluorescence of the choriocapillaris which at 1 week is identical in size to the area of the treatment spot used, consistent with a direct occlusive effect. However, clinical doses of PDT leave the overlying RPE and the neurosensory retina undamaged (18). Choroidal perfusion changes in the photosensitized area are considered transient, with restoration occurring within 3 months (17, 19). As our study protocol included FA/ICG examination 1 month after the treatment, we could not evaluate this phenomenon at 1 week when choriocapillaris hypoperfusion is most prominent. A combination of PDT and subsequent feeder vessel laser coagulation using standard photocoagulation wavelengths has been used in the treatment of CNV in AMD (7,12) and CNV secondary to choroidal rupture after blunt trauma (20). Interestingly, a study by Piermarocchi (21) showed that previous PDT significantly improves the ability to detect the feeder vessel of the CNV. The PDT treatment results in decreased blood flow to the choriocapillaris, most likely reduces angiographic "noise" in and around the remaining CNV, which can explain a better visualization of the still patent CNV vasculature.

The present study investigates the safety and efficacy of using PDT to directly occlude feeder vessels in subfoveal CNVs in patients with exudative macular degeneration. There is only one similar case reported in the literature (12) with report of visual improvement. As we do not precisely know the amount of energy necessary for feeder vessel closure we chose a dose escalating study approach. Dose escalation was achieved by increasing the treatment time of the standard 50 J/cm^2 dose delivery. We held the systemic drug dose and timing of the treatment the same and increased the light dose in a dose-escalating manner.

In our group the most common feeder vessel pattern was its insertion in CNV membrane from the nasal side (the "racket-like pattern")(Figs.1a, 2b) which is consistent with previous studies (3). One patient had vessel supplying CNV from the temporal side and in one (Fig. 3a) the vessel originated from the choroidal vascular bed directly beneath the CNV and was hidden by the membrane as soon as it was filled with dye (the "umbrella-like pattern"). The first examination after PDT treatment to the feeder vessels showed that patients in the first light dose group had no decrease in CNV perfusion after feeder vessel treatment with verteporfin; angiography revealed that the feeder vessels remained perfused. In the second light dose group, we saw feeder vessel closure in 1 patient (Fig. 1b) and hypoperfusion in another and permanent closure in the last one. In the third escalating light dose, one patient had hypoperfusion of a feeder vessel (Fig. 3b) and the other, with an umbrella-like pattern feeder vessel, had no treatment effect. At the last follow-up feeder vessels in all study patients

were either still perfused or re-perfused. We therefore have not seen any trend to associate a particular light dose with the anatomic outcome.

Failure of feeder vessel closure after its laser photocoagulation has been previously reported (3). The phenomenon of non-occlusion and/or reperfusion after PDT treatment is well known. Schmidt-Erfurth et al. (17) showed that vessel occlusion after PDT is not complete and that the CNV complex remains patent at the feeder vessel level in 50% of treated patients. Multiple PDT applications within short intervals have been shown to reduce the vessel patency in CNV but did not influence the frequency of recurrence of new vessels. Tomographic analysis also revealed loss of the superficial choriocapillaris layer and maintenance of perfusion of larger choroidal vessels. In addition, the above-mentioned histopathologic study in rats (10) showed reperfusion of the feeder vessel 1 week after its occlusion. Based on these data it is tempting to speculate that a similar mechanism occurred in our patients in early post-treatment period.

Provided that high enough laser energy is used to occlude the FV there are other factors associated with blood supply to CNV, namely feeder vessel number and width. Even though strict inclusion criteria in this study included the presence of only one vessel, it is possible that CNV membranes were nurtured by more than one feeder vessel. In a histopathologic study of choroidal neovascular membranes by Green et al. (22) 54% of examined eyes had 2 or more vascular sources. It is therefore very likely that in human CNV smaller feeder vessels are present but are not angiographically visible. The average width of feeder vessels on ICG angiography in a study by Staurenghi was 81 μm

and one of the possible reasons for treatment failure in the past was attributed to treatment directed only to larger vessels (3). Similarly, large CNV can be nurtured by multiple capillaries traversing Bruch's membrane in addition to an arteriole from the choroid (23).

It is interesting that, although we were able to only partially occlude the feeder vessels as evidenced by ICG angiography, functional outcome in our patients showed improvement in VA. Only one patient in the first light dose group lost 1 line of VA, however, there was an average gain of 2.6 ETDRS lines (13 letters) for the rest of the group. There was a trend ($p=.075$) toward better VA after treatment. Most of the improvement was noticed in treatment groups with the second and third light doses. Subanalysis eliminating the lowest light dose showed significant improvement ($p=.030$) between pre- and post-PDT VA results with almost doubling of the visual angle. Other morphological outcomes showed lessening of retinal edema by stereoscopic examination in three patients at the three month post treatment time point. There was also a smaller area of fluorescein leakage when we compared pre- and post-treatment fluorescein angiogram frames with borderline significance for the higher treatment doses.

These results indicate that PDT treatment of feeder vessels has an impact on the course of the disease as the results of natural history of fresh exudative AMD are much more discouraging. Our study shows no evidence of retinal damage outside the treatment spot even at the higher doses of light. Further studies at high doses of light appear to be warranted.

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LEGENDS TO FIGURES

Fig. 1a - Fluoroangiographic/ICG image of the posterior pole of the right eye in a patient before verteporfin photodynamic treatment of the feeder vessel complex. Arrow points to the treated spot.

Fig. 1b - Fluoroangiographic/ICG image of the posterior pole of the same patient 1 month after verteporfin photodynamic treatment with 50 J/cm^2 light dose. Arrow shows closure of the feeder vessel complex.

Fig. 1c - Fluoroangiographic/ICG image of the posterior pole of the same patient 3 months after verteporfin photodynamic treatment with 50 J/cm^2 light dose. Arrow shows reperfusion of the feeder vessel complex.

Fig. 2a - Fluoroangiographic/ICG image of the posterior pole of the left eye before verteporfin photodynamic treatment of the feeder vessel complex. Arrow points to the treated spot.

Fig. 2b - Fluoroangiographic/ICG image of the posterior pole of the same patient 1 month after verteporfin photodynamic treatment with 100 J/cm^2 light dose. Arrow shows hypoperfusion of the feeder vessel.

Fig. 2c - Fluoroangiographic/ICG image of the posterior pole of the same patient 3 months after verteporfin photodynamic treatment with 100 J/cm^2 light dose. Arrow shows reperperfusion of the feeder vessel.

Fig. 3a - Fluoroangiographic/ICG image of the posterior pole of the left eye before verteporfin photodynamic treatment of the feeder vessel complex. Arrow points to the treated spot, arrowheads delineate borders of the choroidal neovascular membrane.

Fig. 3b - Fluoroangiographic/ICG image of the posterior pole of the same patient 1 month after verteporfin photodynamic treatment with 125 J/cm^2 light dose. Arrow shows no change in perfusion of the feeder vessel, arrowheads delineate borders of the choroidal neovascular membrane.

Fig. 3c - Fluoroangiographic/ICG image of the posterior pole of the same patient 3 months after verteporfin photodynamic treatment with 125 J/cm^2 light dose. Arrow shows no change in perfusion of the feeder vessel, arrowheads delineate borders of the choroidal neovascular membrane.

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Table.1. Patients demographic characteristics with (pre-) and post-treatment visual acuity and light dose regimen in verteporphin enhanced feeder vessel therapy group.

Patient	Sex	Treated eye	Dose (J/cm^2)	Pre-Tx area of leakage (mm^2)	Post-Tx area of leakage (mm^2)	Pre-Tx ETDRS	Post-Tx 1 week ETDRS	Post-Tx 4 weeks ETDRS	Post-Tx 3 months ETDRS
1.	M	OD	50	36.46	29.10†	20/100	20/100	20/100	20/50†
2.	M	OS	50	12.13	15.59†	20/160	20/125	20/160	20/200†
3.	F	OD	100	3.75	3.58†	20/50	20/63	20/50	20/32*
4.	F	OS	100	0.73	0.51†	20/80	20/80	20/125	20/63*
5.	F	OD	100	8.11	7.06†	20/400	20/100	20/100	20/100*
6.	M	OS	125	9.75	5.52†	20/200	20/160	20/160	20/160*
7.	F	OS	125	16.18	14.11†	20/400	6'/200	20/200	20/125*

OD - right eye, OS - left eye, M - male, F - female, Tx - treatment, ETDRS - Early Treatment Diabetic Retinopathy Study visual acuity chart, † - p-value pre-treatment versus 3 months post-treatment for the entire group ($p>0.05$), * - p-value pre-treatment versus 3 months post-treatment excluding the lowest energy dose ($p<0.05$),

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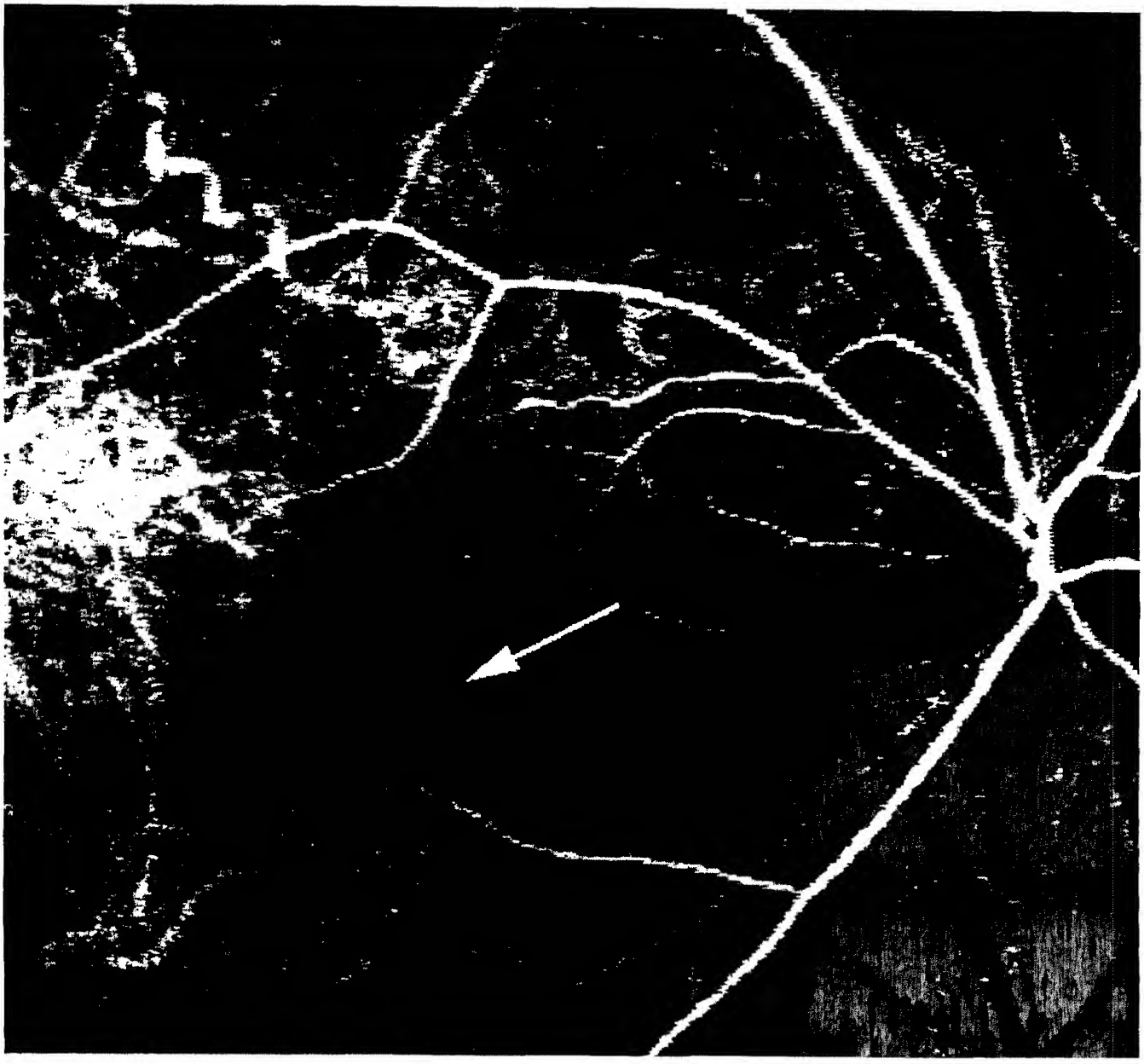

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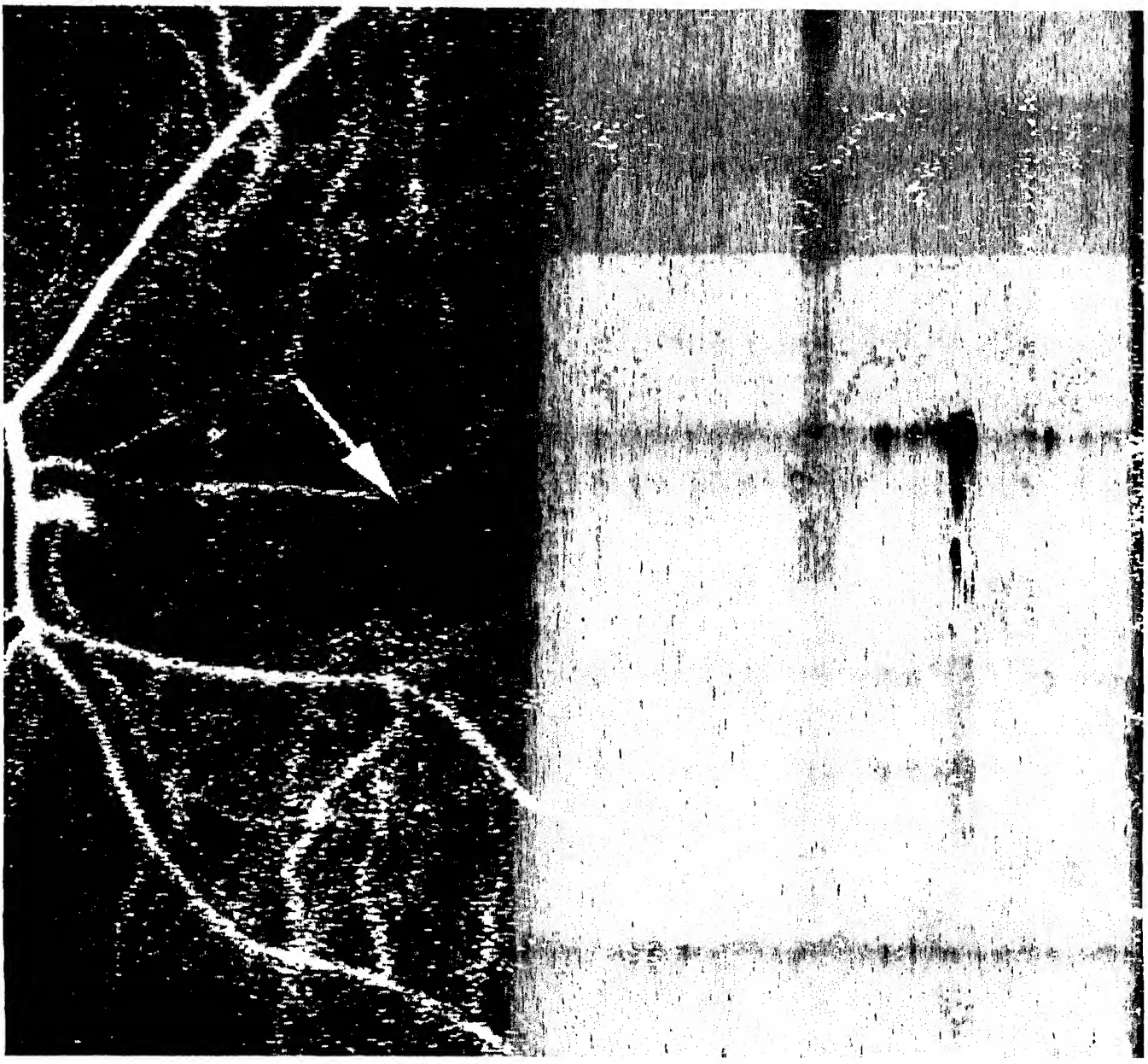

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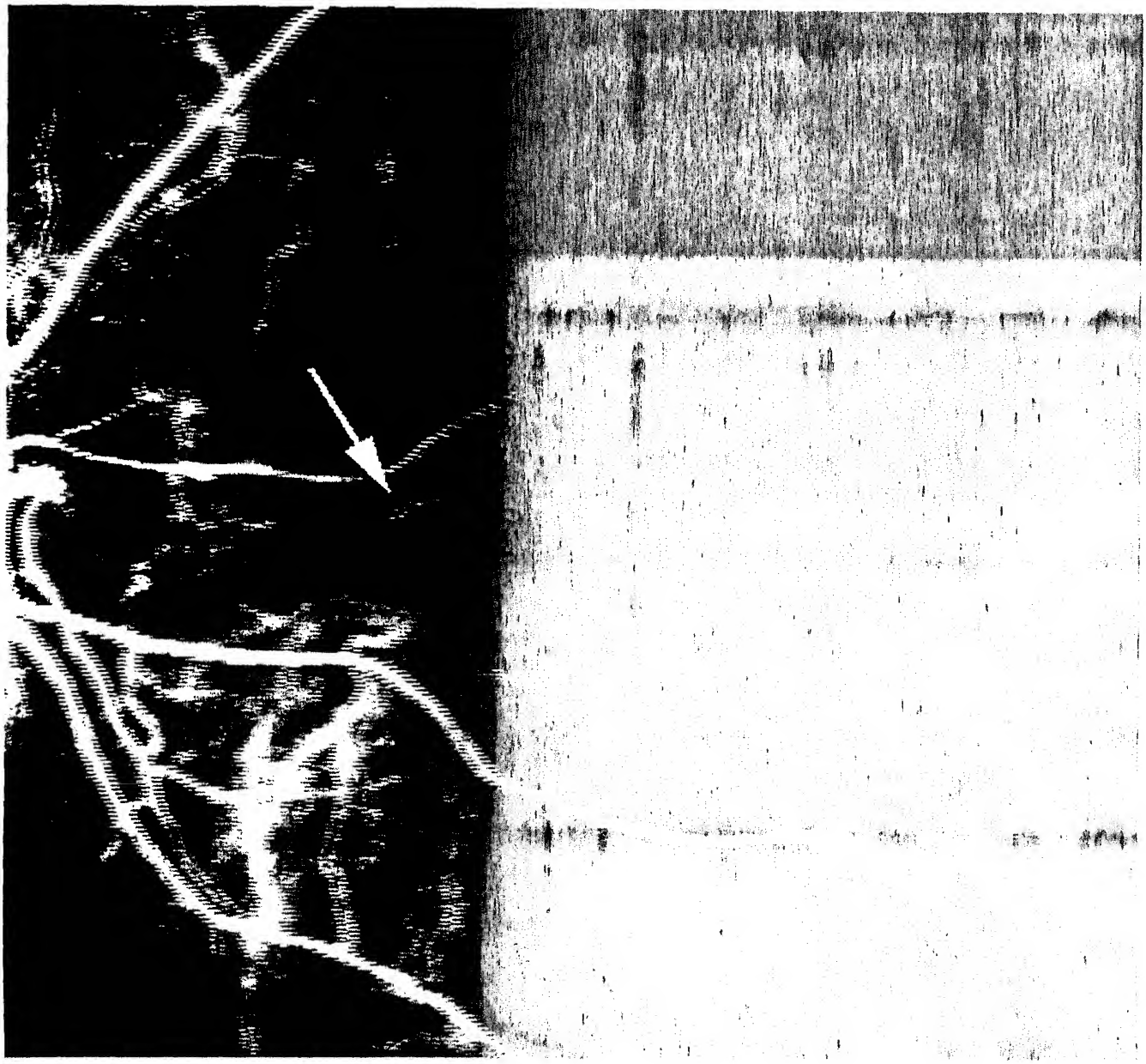

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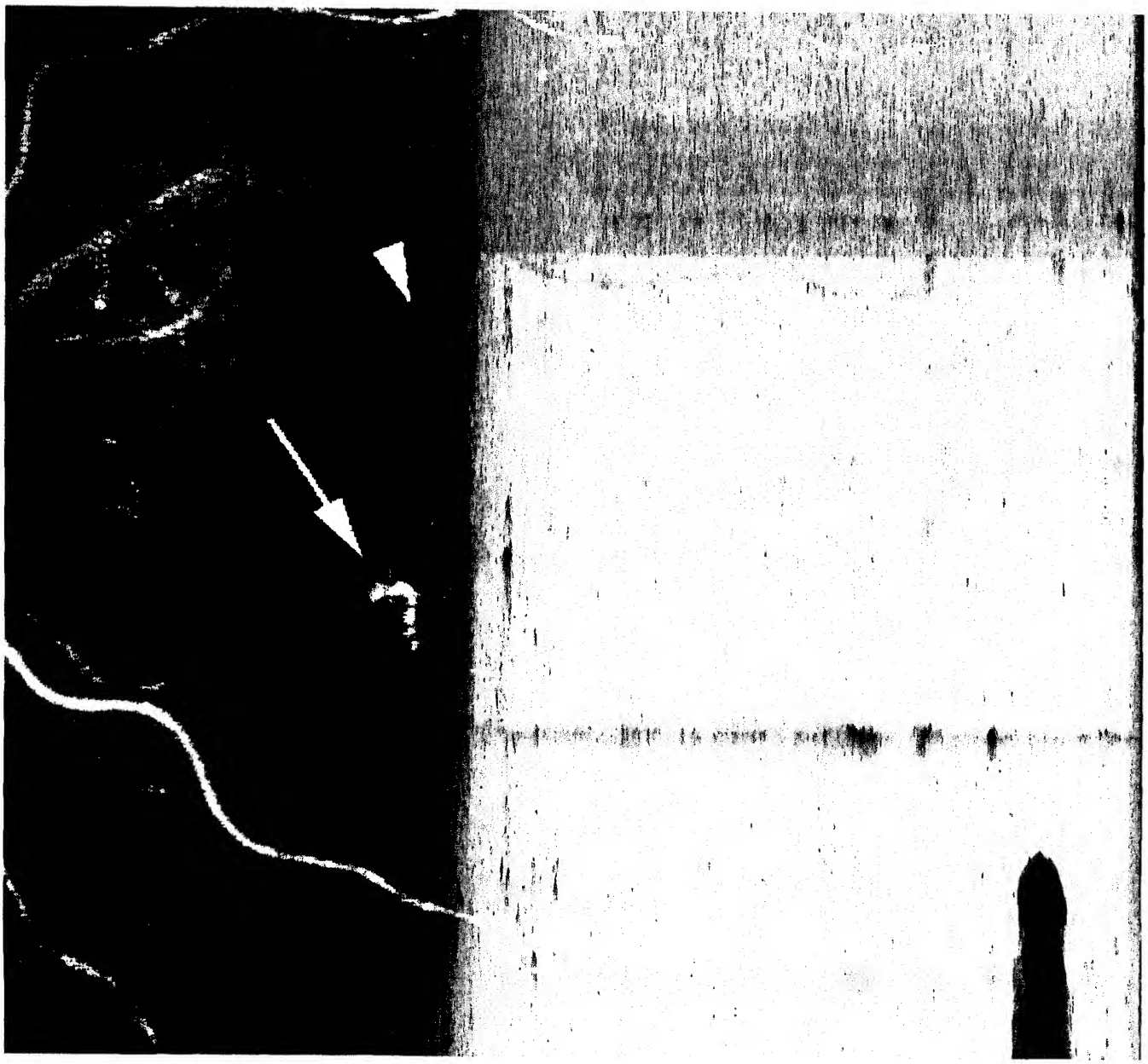

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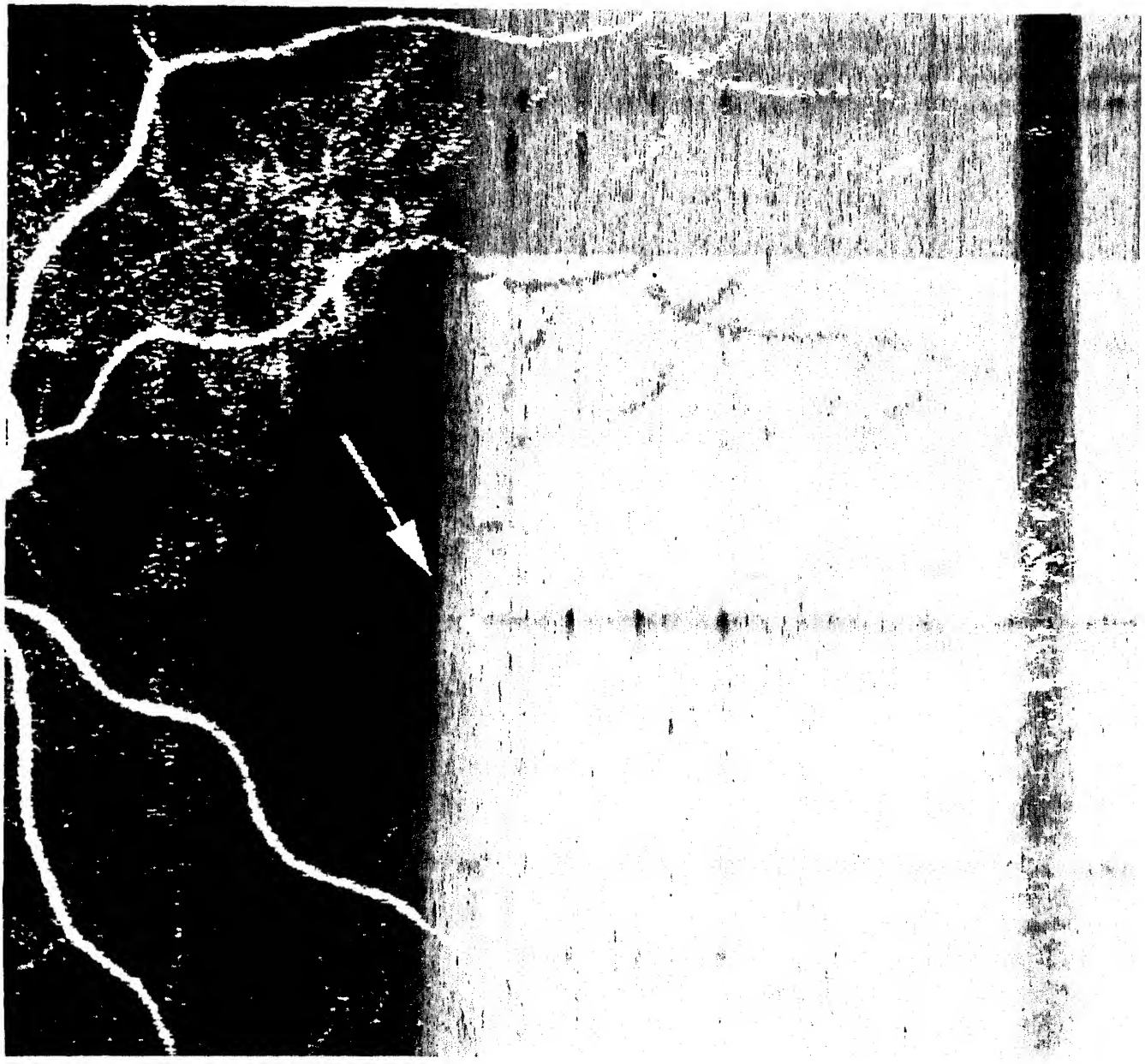

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